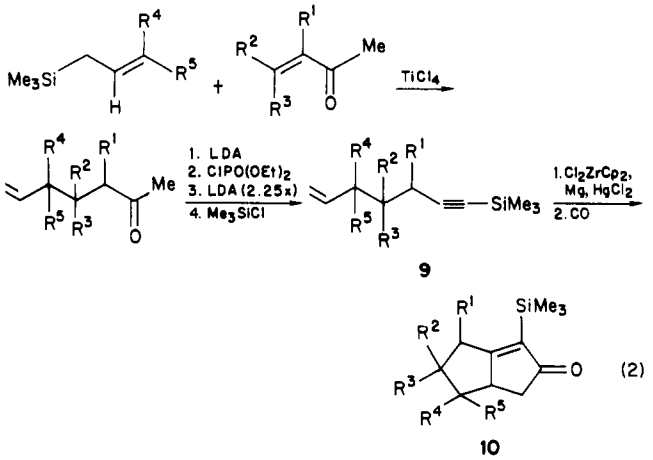
Table I. Zirconium-Promoted Bicyclization of Enynes

enyne (CH_2=CHR^1C≡CZ)		zircona-cyclopentene		cyclopentenone	
R^1	Z	time,[a] h	yield, %	time,[b] h	yield,[c] %
$-(CH_2)_3-$	$SiMe_3$	12	95[d]	1	55–65 (65–75)
$-Me_2C(CH_2)_2-$	$SiMe_3$	18	*e*	4	62
$-CH_2Me_2CCH_2-$	$SiMe_3$	18	*e*	4	50
$-(CH_2)_4-$	$SiMe_3$	12	90–100[d]	3	60
12		18	*e*	2	55

[a] At room temperature. [b] At 0 °C. [c] Isolated yield. The number in parentheses is a GLC yield. [d] Isolated yield. [e] The corresponding figure was not observed.

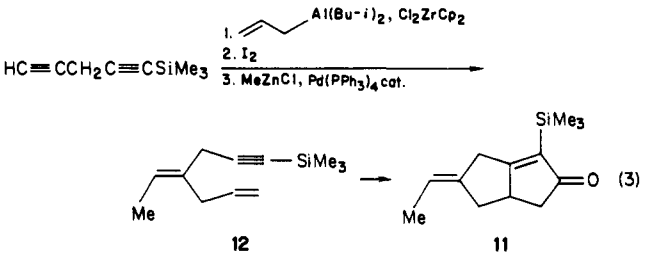
but the product was extensively contaminated with a couple of byproducts one of which presumably is **8**.

While the full scope of the cyclization–carbonylation sequence is yet to be delineated, the experimental data summarized in Table I indicate that the method shows considerable promise as a synthetic tool. It should be noted that the required acyclic precursors are readily available in most cases. For example, various alkyl-substituted 7-silylhept-1-en-6-ynes (**9**) required for preparing **10** can be conveniently prepared via the Sakurai conjugate allylation[11] and conversion of methyl ketones into silylalkynes[12] (eq 2).



9 **10** (2)

In conjugation with our other projects directed toward highly selective syntheses of exocyclic alkenes of biological interest, we sought a convenient route to bicyclo[3.3.0]oct-1(2)-en-3-one derivatives containing a stereodefined exocyclic alkenyl group in the C-7 position, such as **11**. To this end, we prepared the required precursor **12**[8] as an isomerically >97% pure substance in 50% yield from 1-(trimethylsilyl)-1,4-pentadiyne[13] via Zr-catalyzed allylalumination[14] with allyldiisobutylalane–Cl_2ZrCp_2 and methylation. No difficulty was encountered in converting **12** into isomerically >97% pure **11**[8] in 55% yield (eq 3). Retention of configuration during the conversion of **12** into **11** is assumed.



12 **11** (3)

(11) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.
(12) Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A., Jr. *J. Org. Chem.* **1980**, *45*, 2526.
(13) This compound was prepared in 64% yield by a procedure reported in the literature (Verkrnijsse, H. D.; Hasselaar, M. *Synthesis* **1979**, 292).
(14) Miller, J. A.; Negishi, E. *Tetrahedron Lett.* **1984**, *25*, 5863.

The scope of the bicyclization reaction and utilization of α-silylcyclopentenones are being investigated in detail.

Acknowledgment. We thank the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support. We also thank Professor J. E. Bercaw of California Institute of Technology for informing us of their unpublished results.

Lewis Acid Assisted Condensations between a 5-Methoxyisoxazolidine and Silicon-Based Nucleophiles: γ-Amino Alcohol Building Block in the Synthesis of Agroclavine I

Alan P. Kozikowski* and Philip D. Stein[†]

Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

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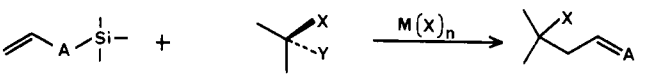
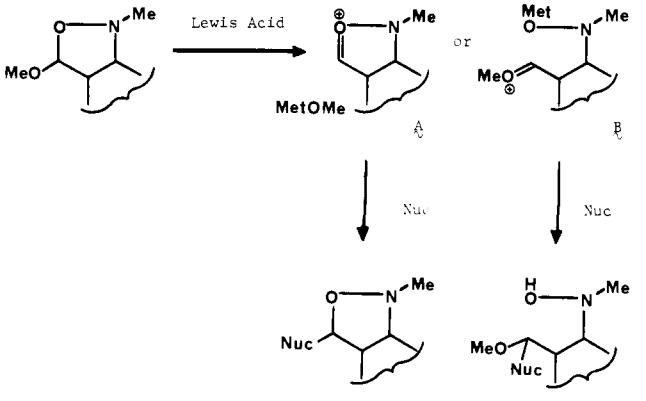
The Lewis acid assisted reactions of various storable nucleophiles (e.g., enol silyl ethers, allyl- and vinylsilanes, and stannanes) with onium ion intermediates formed by the reaction of a metal salt with an appropriate substrate (e.g., aldehydes, ketones, acetals, hemithioacetals, hemiaminals, thioacetals, and hemithioaminals) constitute a selective method of C–C bond formation which continues to grow in both popularity and practicality.[1]



X, Y = N, O, S, Se, halogen
A = C, O

In further developing approaches to the ergot alkaloids,[2] we envisioned that one could obtain appropriately substituted precursors to the tetracyclic members of this family by carrying out Lewis acid assisted condensation reactions between an appropriately constituted 5-methoxyisoxazolidine and an enol silyl ether. Of course, such an isoxazolidine derivative could react through either the cyclic oxonium ion intermediate A or the acyclic oxonium ion species B (Scheme I). The formation of such oxonium

Scheme I



[†] Andrew Mellon Predoctoral Fellow of the University of Pittsburgh, 1981–1983.

(1) Weber, W. P. "Silicon Reagents for Organic Synthesis"; Springer-Verlag: Berlin, 1983. Colvin, E. W. "Silicon in Organic Synthesis"; Butterworths: London, 1981. Sakurai, H. *Pure & Appl. Chem.* **1982**, *54*, 1. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.
(2) Kozikowski, A. P.; Greco, M. N. *J. Am. Chem. Soc.* **1984**, *106*, 6873 and references therein.

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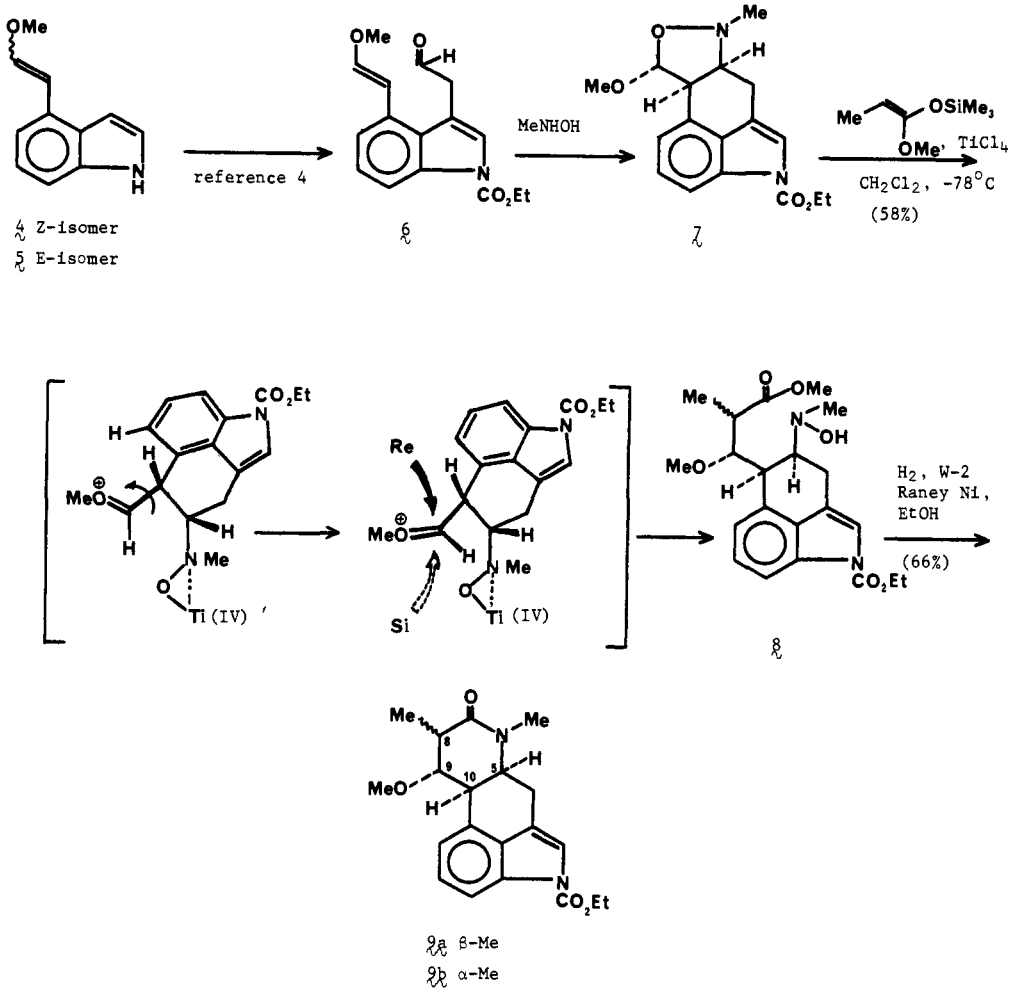
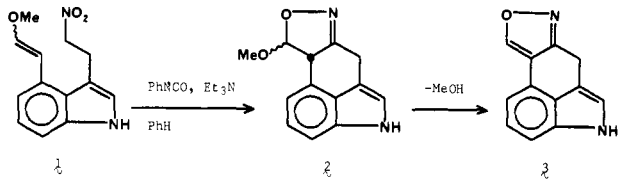
Scheme II



ions might be selected through the use of specific metal salts and possibly reaction solvents (wherein a thermodynamic sorting between the oxonium ions could take place).

To prepare the required isoxazolidine, we initially tried to make use of the intramolecular nitrile oxide cycloaddition product formed from **1**.[3] However, owing to the rather facile loss of methanol from the cycloaddition product **2**, which results in formation of the aromatic isoxazole **3**, we opted to carry out an



intramolecular nitrone cycloaddition reaction instead. The nitrone cyclization does provide directly the desired tetracyclic intermediate in the correct oxidation state.

The enol ether **4** available from indole-4-carboxaldehyde and (methoxymethylene)triphenylphosphorane[3] was isomerized to the *E* isomer **5** with mercuric acetate/methanol in benzene (3:1 ratio at equilibrium; separated by HPLC on a Waters Prep 500). The pure *E* isomer was then converted along lines previously set forth by Oppolzer to the aldehyde **6**.[4] Condensation of this aldehyde with *N*-methylhydroxylamine afforded the nitrone intermediate which was heated to effect cyclization to solely the cis-fused isoxazolidine **7** ($J_{5,10}$ = 5.5, $J_{9,10}$ < 1 Hz).

On exposure of this isoxazolidine to the ketene silyl acetal of methyl propionate[5] and $TiCl_4$ in CH_2Cl_2 at −78 °C followed by a water quench, an isomeric mixture of methoxy esters **8** was generated. Upon N–O bond hydrogenolysis, two methoxy lactams were isolated which by ^1H NMR analysis differed only in their configurations at C-8 (**9a** $J_{8,9} \cong 9$, $J_{9,10} \cong 11$, $J_{5,10} \cong 5$ Hz; **9b** $J_{8,9}$ = 5.6, $J_{9,10}$ = 10.3, $J_{5,10}$ = 4.6 Hz).

Apparently, in this instance complexation of $TiCl_4$ to the N–O portion of the isoxazolidine ring leads to rupture of the endocyclic acetal C–O bond. An oxonium ion is generated, which on rotating in the direction indicated by the arrow (this brings the smaller H atom nearer the complexed N–O group) allows for the less obstructed entry of the ketene silyl acetal from the top (*Re*) face as shown. This process thus fixes the stereochemistry of the C-9 center relative to C-5 and C-10.[6] No apparent discrimination between the faces of the ketene silyl acetal is observed in this addition reaction, for the ratio of **9a** to **9b** is 1:1.

When this same reaction was repeated employing zinc triflate as the Lewis acid,[7] a stereoisomeric mixture of isoxazolidines **10a**

(3) Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265. Plieninger, H.; Wagner, C.; Imel, H. *Liebigs Ann. Chem.* **1971**, *743*, 95.

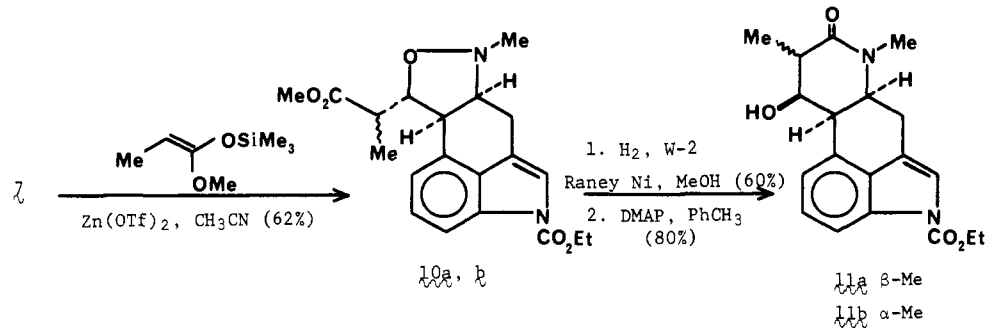
(4) Oppolzer, W. *Heterocycles* **1980**, *14*, 1615. Oppolzer, W.; Grayson, J. I. *Helv. Chim. Acta* **1980**, *63*, 1706. Oppolzer, W.; Grayson, J. I.; Wegmann, H.; Urrea, M. *Tetrahedron* **1983**, *39*, 3695.

(5) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

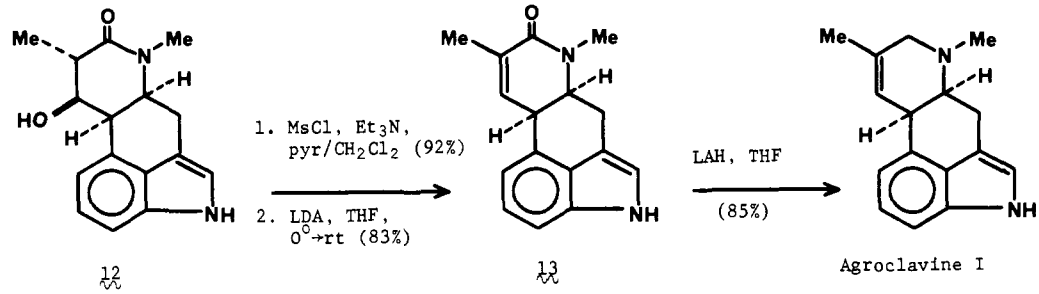
(6) Allyltrimethylsilane also reacts with **7** in the presence of $AlCl_3$ to deliver a product which contains a methoxy group. Its mechanism of formation must thus be related to that suggested for the conversion of **7** to **8**.

(7) Zinc triflate has proven to be an effective catalyst for a number of synthetic operations. Thioketalization: Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169. Pyranone formation: Kozikowski, A. P.; Li, C. S. *J. Org. Chem.*, in press. α-Phenylthiopyrrolidine formation: ref 2. Indole synthesis: Kozikowski, A. P.; Cheng, X.-M.; Li, C. S.; Scripko, J. G. *Isr. J. Chem.*, in press.

Scheme III



Scheme IV



and **10b** resulted. Proof that these compounds differed only in the stereochemistry of their C-8 centers was gleaned by hydrogenating the mixture and cyclizing the resulting δ-amino esters to the corresponding lactams (**11a**, $J_{8,9} = 4$, $J_{9,10} < 1$, $J_{5,10} = 5.7$ Hz; **11b**, $J_{8,9} < 1$, $J_{9,10} = 2.1$, $J_{5,10} = 5.5$ Hz). Accordingly, the cyclic oxonium ion formed from **7** suffers addition only from its *Si* face (convex face addition). Again, no discrimination is observed for the faces of the ketene silyl acetal.

To demonstrate the utility of this novel isoxazolidine → γ-amino alcohol transformation in synthesis, **11b** was further converted to the newly isolated ergot alkaloid agroclavine I. The *N*-carboethoxy group of **11b** was first removed (KOH, MeOH, 85%), as its removal later on proved deleterious to the subsequent LAH reduction. Upon mesylation and LDA promoted elimination, **12** was transformed to the enamide **13**. Attempts to effect this elimination reaction with DBU in refluxing benzene led instead to generation of the deconjugated (Δ^9) isomer. Such an isomerization event is noteworthy, for it could prove valuable to the procurement of the ergot alkaloid lysergine.[8]

From **13**, a simple LAH reduction in refluxing tetrahydrofuran led to the desired, C,D-cis-fused ergot, agroclavine I (Scheme IV). The UV, IR, NMR and mass spectra of the synthetic material matched precisely that available from the literature.[9]

In conclusion, we have demonstrated that one can utilize the Lewis acid assisted condensation of silicon-based nulceophiles with an alkoxy-substituted isoxazolidine substrate so as to access functionalized γ-amino alcohols.[10] One can thus extend the Lewis acid promoted C–C bond-forming methodology to heterocyclic systems containing adjacent ring heteroatoms.[11] The divergent behavior of the zinc and titanium salts in the course of the reactions reported is presumably a function of the charge/radius ratio of the metal as well as of ability of the solvent to participate through complexation to the metal and through interaction with the onium ion intermediate.

Acknowledgment. We are indebted to the National Institutes of Health for their generous support of these investigations.

Registry No. 1, 95484-69-8; **2**, 95484-70-1; **3**, 95484-71-2; **4**, 73805-09-1; **5**, 95484-72-3; **6**, 95484-73-4; (±)-**7**, 95484-74-5; (±)-**8** (isomer 1), 95484-75-6; (±)-**8** (isomer 2), 95586-11-1; (±)-**9a**, 95484-76-7; (±)-**9b**, 95484-77-8; (±)-**10a**, 95484-78-9; (±)-**10b**, 95586-09-7; (±)-**11a**, 95484-79-0; (±)-**11b**, 95484-80-3; (±)-**12**, 95484-81-4; (±)-**13**, 95484-82-5; $CH_3CH{=}C(OCH_3)OTMS$, 34880-70-1; (±)-agroclavine **I**, 95586-10-0; phenyl isocyanate, 103-71-9.

Supplementary Material Available: Melting points, IR, ^1H NMR, and high-resolution mass spectral data for compounds **4**/**5**, **7**, **10a**, **b**, **11b**, **12**, **13**, and agroclavine I (3 pages). Ordering information is given on any current masthead page.

(8) For other recent efforts in the ergot area, see: Kruse, L. I.; Meyer, M. D. *J. Org. Chem.* **1984**, *49*, 4761 and references therein.

(9) Sakharovsky, V. G.; Kozlovsky, A. G. *Tetrahedron Lett.* **1984**, *25*, 109. Kozlovsky, A. G.; Solovieva, T. F.; Sakharovsky, V. G.; Adanin, V. M. *Prikl. Biokhim. Mikrobiol.* **1982**, *18*, 535.

(10) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199.

(11) The use of silicon reagents in the functionalization of heterocycles containing a single heteroatom in the ring has proven quite popular, especially in the carbohydrate area: Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, **25**, 2383 and references therein.

Phenoxide-Directed Ortho Lithiation

Gary H. Posner* and Karen A. Canella

Department of Chemistry
The Johns Hopkins University
Baltimore, Maryland 21218

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Heteroatom-facilitated ortho lithiation is a very popular and powerful technique which can lead to regiospecific attachment of an electrophile ortho to a heteroatom-containing substituent on an aromatic ring.[1] Recently some significant and creative applications of this methodology to the synthesis of several different classes of aromatic intermediates[2] and natural products[3] have been

(1) (a) Gilman, H.; Morton, J. W., Jr. *Org. React.* (*N.Y.*) **1954**, *8*, 258. (b) Gschwend, H. W.; Rodriguez, H. R. *Ibid.* **1979**, *26*, 1 and references therein. (c) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 965. (d) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

(2) (a) Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515. (b) Uemura, M.; Isobe, K.; Take, K.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 3855. (c) Shankaran, K.; Snieckus, V. *Ibid.* **1984**, *49*, 5022. (d) Narasimhan, N. S.; Ranade, A. C.; Deshpande, H. R.; Gokhale, U. B.; Jayalakshmi, G. *Synth. Commun.* **1984**, *14*, 373.

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